REMARKS

Claims 1, 3-8, 13-16, 18-22, 28-30, 36-44, 46, 48-66, 68-72, 74, 76-85, 88, 91-95, 98-100, 133-137 are pending. Claims 1, 4, 8, 11, 13, 28-30, 39, 42, 48, 52-55, 57, 58, 64, 65, 70, 74, 76, 83, 85, 88, 93, 95, 99 and 100 have been amended. Claims 2, 3, 9, 10, 12, 17, 23-27, 31-35, 49, 60, 68-69, 75, 79-82, 84, 86, 87, 89-90, 96, 97, 101-132 and 138 have been cancelled. New claim 139 has been added. Thus, claims 1, 4-8, 11, 14-16, 18-22, 28-30, 36-44, 46, 48, 50-59, 61-66, 70-72, 74, 76-78, 83, 85, 88, 91-95, 98-100, 133-137 and 139 are presented for prosecution. No new matter has been added by way of these amendments. Entry of the amendment is respectfully requested.

Objection to Claim 11

The Office objected to claim 11 as being dependent upon a rejected base claim, but found the subject matter of the claim allowable if the claim was rewritten in independent form incorporating the limitations of all intervening claims. Applicants thank the Office for this offer but decline to take the suggested action. Applicants submit that claim 1, from which claim 11 depends, is allowable.

Sequence Listing

The Office alleged that the present application failed to comply with the requirements of 37 CFR §§ 1.821-1.825 because the peptide sequence eon page 32, line 1, was not identified by a sequence identification number. Also, some of the sequences provided in Figure 24 were not identified by sequence identification numbers. The specification and the figures have been amended to supply those sequence identification numbers inadvertently omitted. Also Figure 24 was amended to reflect the appropriate number of bases in SEQ ID NO: 1 (532). A substitute sequence listing and the appropriate documentation is also supplied with this response.

Due to errors found in the previously submitted Sequence Listing, applicants submit herewith a substitute paper copy of the Sequence Listing, pages 1-25, and substitute computer readable form (labeled "CRF") of the Sequence Listing in CD-R format, in compliance with 37 C.F.R. §1.821(c), and §1.825(a) and (b). The substitute sheets of the Sequence Listing and the

substitute computer readable form labeled "CRF" submitted herewith, in accordance with 37 C.F.R. §1.825(a) and (b), respectively, are the same and contain no new matter. Accordingly, entry of the substitute Sequence Listing into the above-captioned case is respectfully requested.

Enablement

Claims 1, 3-8, 13-16, 18-22, 28-30, 36-44, 46, 48-49, 51-53, 55, 57-66, 68-72, 74, 76-85, 88, 91-95, 98-100 and 133-137 stand rejected under 35 USC § 112, first paragraph, for alleged not being supported by an enabling disclosure. Specifically, the Office alleged that the specification does not reasonably provide enablement for any method to modulate the expression of a target gene with any zinc finger protein capable of binding to any 18 nucleotides with the target gene. Applicants respectfully disagree.

The test for enablement requires that the specification teach those of ordinary skill in the art how to make and use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993). Enablement "is not precluded even if some experimentation is necessary, although the amount of experimentation needed must not be unduly extensive." *See Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367 (Fed. Cir. 1986).

Applicants thank the Office for the helpful advice regarding claim amendments. However, Applicants respectfully disagree with the Office regarding the proper scope of the pending claims and the enabling disclosure supporting those claims. As such, Applicants have adopted most of the claim amendments proposed by the Office in the Action. Applicants cannot accept limiting the pending claims to target nucleotide sequences of the formula $(GNN)_6$, wherein N is any one of the A, T, C or G.

The Office takes the position in the Action that the present specification is enabling only for synthetic zinc finger proteins that are designed to target unique sequences of the formula $(GNN)_6$, wherein N is any one of the A, T, C or G. The Office supported their position by citing commentary from Choo & Isalan (*see* Current Opinion in Structural Biology (2000) 10:411-418). The Office argues that those of ordinary skill in the art would not be able to practice the claimed invention without "trial and error" experimentation, which is considered "undue". Applicants disagree with the Office's characterization of the state of the art.

Choo & Isalan do cast a relatively negative light on the relevant field on the first page of their article. But their point of view improves as the article continues. On page 412, first column, the authors recognize the importance that synergistic interactions between different adjacent zinc fingers and the target DNA play in moving away from the $(GNN)_6$ formula. The authors go on to cite an alternative method of zinc finger engineering that produces "zinc finger polymers that recognize a greater diversity of nucleotide sequences." (*Id.* at 412, second column.)

Choo & Isalan also tout a "novel" zinc finger engineering strategy that is "not limited to producing fingers that bind particular subsets of DNA sequences." (*Id.* at 413, first column.) The authors go on to state that "[w]e believe that it will be possible to target any gene promoter using this method." (*Id.*) The method referenced by the authors issued on June 8, 2004 as U.S. Patent No. 6,746,838. Thus, contrary to the Office's characterization of the state of the art, skilled artisans would have been able to design synthetic zinc finger binding proteins to target any sequence of interest without having to engage in undue experimentation.

Furthermore, the teachings of the specification itself provide sufficient guidance to those of ordinary skill in the art to practice the full scope of the claimed invention without undue experimentation. The specification provides detailed guidance regarding the design of synthetic zinc finger DNA binding proteins at page 28, line 17 to page 30, line 22. This guidance, taken with that provided in the Examples and with the state of the art at the relevant time period clearly demonstrate that the pending claims are adequately supported by an enabling disclosure. Therefore, the reasons supporting the present rejection have been overcome and the pending claims are in condition for allowance.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 278012001420.

Respectfully submitted,

Dated: December 10, 2004 By: _____

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cgcaagaggcataccaaaatccataccggtgagaagccctatgcttgccctgtcgagtcctgcgatcgccgcttttctaagtcgg
ctgatctgaagcgccatatccgcatccacacaggccagaagcccttccagtgtcgaatatgcatgcgtaacttcagtcgtagtga
ccaccttaccacccacatccgcacccacacaggcgagaagccttttgcctgtgacatttgtgggaggaagtttgccaggagtgat
gaacgcaagaggcataccaaaatccatttaagacagaaggactctagaactagtggccaggccggccagtacccgtacgacg
ttccggactacgcttcttgaaagcttggtaccgagctcggatcccccgaatttccccgatcgttcaaacatttggcaataaagtttctt
aagattgaatcctgttgccggtcttgcgatgattatcatctaatttctgttgaattacgttaagcatgtaataattaacatgtaatgcatg
acgttatttatgagatgggtttttatgattagagtcccgcaattatacatttaatacgcgatagaaaacaaaatatagcgcgcaaacta
ggataaattatcgcgcgcggtgtcatctatgttactagatccgggaattccggaccggtaccagcggcc

Total:	3068 bp
ZmUbi promoter:	44 bp to 2026 bp
SID repression domain:	2066 bp to 2173 bp
Nuclear localization signal:	2174 bp to 2194 bp
Six finger ZFP2C7:	2207 bp to 2735 bp
HA eptitope tag:	2762 bp to 2791 bp
Nos terminator:	2820 bp to 3112 bp

(6) Sequence of 6X2C7 binding site (SEQ ID NO:6):

Cgtgctagcgcgtgggcggcgtgggcgaacaagcgtgggcggcgtgggcgaacaagcgtgggcggcgtgggc
gactagtgctagcgcgtgggcggcgtgggcgaacaagcgtgggcggcgtgggcgaacaagcgtgggcggcgtgggcgac
tagtg

Total: 155 bp

(7) Sequence of 3 finger protein C7 (SEQ ID NO:73):

Atggcccaggcggccctcgagccctatgcttgccctgtcgagtcctgcgatcgccgcttttctaagtcggctgatctg
aagcgccatatccgcatccacacaggccagaagcccttccagtgtcgaatatgcatgcgtaacttcagtcgtagtgaccacctta
ccacccacatccgcacccacacaggcgagaagccttttgcctgtgacatttgtgggaggaagtttgccaggagtgatgaacgca
agaggcataccaaaatccatttaagacagaaggactctagaactagtggccaggccggccaggctagc

Total: 314 bp

(8) Amino acid sequence of 3 finger protein C7 (SEQ ID NO:74):

ANNOTATED MARKED-UP DRAWING

Maqaalepyacpvescdrrfsksadlkrhirihtgqkpfqcricmrnfsrsdhltthirthtgekpfacdicgrkfar sderkrhtkihlrqkdsrtsgqagqas

Total: 105 aa

(9) Sequence of zinc finger protein ZFPAp3 binding site (SEQ ID NO:7):

GAT GGA GTT GAA GAA GTA

Total: 18 bp

(10) Sequence of zinc finger protein ZFPm1 and ZFPm2 binding site m12: (SEQ ID NO:76): GCC TCC TTC CTC CTC TCA CTC

Total: 21 bp

ZFPm1 binding site: compliment strand of 1 to 18

ZFPm2 binding site: compliment strand of 4 to 21

(11) Sequence of zinc finger protein ZFPm3 and ZFPm4 binding site m34 (SEQ ID NO:77):

GCC AAC TAC TAC GGC TCC CTC ACC

Total: 24 bp

ZFPm3 binding site: compliment strand of 1 to 18

ZFPm4 binding site: compliment strand of 7 to 24

(12) Partial sequence of pMal-m1 (1-3300 bp) and zinc finger protein ZFPm1 (2719-3270 bp) (SEQ ID NO:14):

ccgacaccatcgaatggtgcaaaacctttcgcggtatggcatgatagcgcccggaagagagtcaattcagggtggt gaatgtgaaaccagtaacgttatacgatgtcgcagagtatgccggtgtctcttatcagaccgtttcccgcgtggtgaaccaggcca gccacgtttctgcgaaaacgcgggaaaaagtggaagcggcgatggcggagctgaattacattcccaaccgcgtggcacaaca actggcgggcaaacagtcgttgctgattggcgttgccacctccagtctggccctgcacgcgccgtcgcaaattgtcgcggcgat taaatctcgcgccgatcaactgggtgccagcgtggtggtgtcgatggtagaacgaagcggcgtcgaagcctgtaaagcggcg gtgcacaatcttctcgcgcaacgcgtcagtgggctgatcattaactatccgctggatgaccaggatgccattgctgtggaagctg cctgcactaatgttccggcgttatttcttgatgtctctgaccagacacccatcaacagtattattttctcccatgaagacggtacgcga ctgggcgtggagcatctggtcgcattgggtcaccagcaaatcgcgctgttagcgggcccattaagttctgtctcggcgcgtctgc

ANNOTATED MARKED-UP DRAWING

cggtctgacaatctcgtccggcaccaacgtactcacaccggtaaaaaaactagtggccaggccggccagtacccgtacgacgt tccggactacgct

Total: 514 bp

Primer F1-f1 of ZFPm1: 2770 bp to 2850 bp

Primer F1-f2 of ZFPm1: 2740 bp to 2790 bp

Primer F2-f of ZFPm1: 2867 bp to 2940 bp

Primer F2-b of ZFPm1: 2824 bp to 2889 bp

Primer F3-b1 ZFPm1: 2916 bp to 2973 bp

Primer F3-b2 ZFPm1: 2953 bp to 3021 bp

Primer F4-f1 of ZFPm1: 3022 bp to 3102 bp

Primer F4-f2 of ZFPm1: 2992 bp to 3042 bp

Primer F5-f of ZFPm1: 3119 bp to 3192 bp

Primer F5-b of ZFPm1: 3076 bp to 3141 bp

Primer F6-b1 of ZFPm1: 3168 bp to 3225 bp

Primer F6-b2 of ZFPm1: 3205 bp to 3273 bp

(13) Sequence of zinc finger protein ZFPm1

(Translated from pMal-m1: 2719-3270 bp) (SEQ ID NO:75):

Aqaalepgekpyacpecgksfsdpghlvrhqrthtgekpykcpecgksfsqrahlerhqrthtgekpykcpec gksfsqssnlvrhqrthtgekpyacpecgksfsrsdnlvrhqrthtgekpykcpecgksfsrsdnlvrhqrthtgekpykcpe cgksfsqaghlashqrthtgkktsgqag

(14) Partial sequence of pMal-m2 (1-3300 bp) and zinc finger protein ZFPm2 (2719-3270 bp) (SEQ ID NO:15):

ccgacaccatcgaatggtgcaaaacctttcgcggtatggcatgatagcgcccggaagagagtcaattcagggtggt gaatgtgaaaccagtaacgttatacgatgtcgcagagtatgccggtgtctcttatcagaccgtttcccgcgtggtgaaccaggcca gccacgtttctgcgaaaacgcgggaaaaagtggaagcggcgatggcggagctgaattacattcccaaccgcgtggcacaaca actggcgggcaaacagtcgttgctgattggcgttgccacctccagtctggccctgcacgcgccgtcgcaaattgtcgcggcgat taaatctcgcgccgatcaactgggtgccagcgtggtggtgtcgatggtagaacgaagcggcgtcgaagcctgtaaagcggcg gtgcacaatcttctcgcgcaacgcgtcagtgggctgatcattaactatccgctggatgaccaggatgccattgctgtggaagctg